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The Safety and Efficacy of Colchicine for the Treatment of Pericarditis

Abstract

BACKGROUND: Colchicine has been traditionally used for the treatment of gout. In just over the last twenty years, colchicine has been gaining interest as a treatment for acute and recurrent pericarditis. A few small studies have addressed the safety and efficacy of this treatment, however, a general agreement has not been reached.

METHODS: A systematic literature review of the studies focusing on colchicine for the treatment of pericarditis, from 1990 to present, was performed using the MEDLINE, CINAHL and Web of Science databases. A modified validity scoring method (0-10) was applied to the studies that qualified through the inclusion and exclusion criteria.

RESULTS: Five studies that focused on colchicine for the treatment of pericarditis met the inclusion and exclusion criteria. There were two randomized, open-label studies (n=120 & n=84) with a validity score of eight. There was one prospective, cohort study (n=58) with a validity score of five. There was one retrospective, multi-center case analysis (n=119) that received a validity score of two, and a prospective case series (n=9) with a validity score of three. All of the studies found colchicine to be effective for the treatment of acute or recurrent pericarditis, with 1 mg daily as the most common dose. There were no reports of serious, adverse reactions to colchicine. Diarrhea was the most common side effect. As a secondary outcome, corticosteroids were found to be an independent risk factor for the recurrence of pericarditis in three of the studies.

CONCLUSION: Based on this systematic review of literature, there is moderate evidence showing colchicine to be safe and effective in the treatment of acute or recurrent pericarditis. However, a larger, double-blinded, randomized-controlled trial is needed to further investigate this potential treatment. There is also some evidence to support corticosteroids as an independent risk factor for the recurrence of pericarditis.

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The Safety and Efficacy of Colchicine for the Treatment of Pericarditis

Scott Murray



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Faculty Advisor: Rob Rosenow PharmD, OD

Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette
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Biography

Scott Murray was born and raised in Traverse City, Michigan. He grew up ski racing, playing tennis, and running around the woods with his other redneck friends. After graduating high school, he moved to Montana for college. In 1999, he received a B.A. in English and Philosophy from the University of Montana. Following college he enjoyed working across the western U.S. as a smokejumper in the summers and as a professional ski patrol at Steamboat Springs and Big Sky Ski Resort during the winter. In 2005, Scott moved to Bozeman, completed the necessary pre-medical prerequisites, worked as a medical assistant at the local community health center, and soon became a member of the Pacific University Class of 2009. He looks forward to getting back to the mountains, working in rural health, and starting a family.

Abstract

BACKGROUND: Colchicine has been traditionally used for the treatment of gout. In just over the last twenty years, colchicine has been gaining interest as a treatment for acute and recurrent pericarditis. A few small studies have addressed the safety and efficacy of this treatment, however, a general agreement has not been reached.

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KEYWORDS: colchicine; pericarditis.

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To my girlfriend, Meghan: Thank you for your daily support and putting up with me. I don't know how you do it.

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The Safety and Efficacy of Colchicine for the Treatment of Pericarditis

Introduction and Background

Pericarditis is characterized by inflammation of the pericardial sac, the pericardium, that lines the outside of the heart.¹ Inflammation of the pericardium may have an infectious etiology or it may be due to a variety of systemic illnesses including: autoimmune disease, uremia, neoplasm, radiation, drug toxicity, hemopericardium, post-cardiac surgery, myocardial or lung disease.¹ It can be acute, chronic or recurrent in nature. If the inflammation has an identifiable cause, then treatment will focus on that specific target. However, most cases have a viral or idiopathic origin, for which only symptomatic, nonspecific treatment is available. Usually, symptomatic treatment of pericarditis consists of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and, in rare cases, immunosuppressants or pericardectomy.¹ Pericarditis may have a recurrence rate as high as 15 to 50 percent after its initial episode, although the incidence of the disease is unclear, most likely due to the non-specific symptoms.²⁻⁵ Some patients experience recurrent or chronic symptoms even after a pericardectomy.⁴ These factors demonstrate a clear need for improved treatment for acute, chronic, and recurrent pericarditis.

Colchicine, a plant alkaloid, has been used for many years to treat acute gout attacks, chronic gout and acute arthritis.^{2, 3, 6-8} It relieves pain in acute gout and it decreases the frequency of repeated attacks, although the mechanism of action is not completely understood.⁶ It is believed that colchicine causes a depolymerization of tubulin, which terminates cell division by disrupting the spindle apparatus. In inhibiting normal cellular function, colchicine decreases the mobility of granulocytes and the synthesis and release of leukotrienes to affected areas in the body. Thus, colchicine has an anti-

inflammatory effect by decreasing the mobility of granulocytes and leukotrienes. This process also appears to reduce the deposition of urate crystals, the key component to gouty inflammation.⁶ For acute attacks of gout, the initial dose is 0.6-1.2 mg, followed by 0.6 mg every one to two hours. For prophylaxis of attacks, the dose is approximately 0.6 mg twice daily.⁹ There are intravenous forms of colchicine, but this study will only focus on the oral form of this drug. The most common side effects are nausea, vomiting and diarrhea.⁶ In rare cases, long-term administration may lead to myopathy, neutropenia, aplastic anemia and alopecia.⁶

In the past two decades, colchicine has drawn increased interest as a new therapy for pericarditis. Similar to gout, colchicine's mechanism of action with pericarditis is not completely understood. However, it appears to work on the same anti-inflammatory pathway by inhibiting the motility of granulocytes and leukotrienes to the pericardium. Along with the treatment of gout and arthritis, colchicine has proven to be effective in the prevention of polyserositis in the hereditary inflammatory disorder, Familial Mediterranean fever.¹⁰ In 1987, Rodriguez de La Serna proposed colchicine as a treatment for difficult cases of recurrent pericarditis.¹⁰ Since that time, several small studies have appeared analyzing the validity of his proposal. Most of the studies looked into colchicine's efficacy in preventing recurrent episodes; however, there are also studies that investigate colchicine in the initial, acute attack. To date, there have been no completed and published double-blinded randomized-controlled trials looking into colchicine as a therapy for acute or recurrent pericarditis.

The purpose of this paper is to perform a systematic review of the current literature on the treatment of pericarditis with colchicine. Due to the limited amount of research on this topic, all aspects of pericarditis and colchicine will be considered. Accordingly, the clinical question remains generalized and asks: Is colchicine effective in the treatment of pericarditis? In reviewing the current literature, the goal is to critically evaluate each selected study, qualitatively compile the results, and determine the safety and efficacy of colchicine in the treatment of pericarditis.

Methods

A complete literature search was performed within the MEDLINE, CINAHL and Web of Science databases, using ‘pericarditis’ and ‘colchicine’ as the keywords. Due to the limited amount of studies in this area, a broad search was conducted with only a few inclusion and exclusion criteria. The inclusion criteria were all multi-patient studies that analyzed colchicine for the treatment of acute or recurrent pericarditis from 1990 to present. The exclusion criteria were any single-patient case reports, expert opinion articles, and studies that used intravenous colchicine or that focused solely on surgical patients. Literature outside of the English language, not available in full text, or completed before 1990 was also excluded.

A JADAD scoring system is one method of uniformly critiquing multiple studies for a meta-analysis or systematic review of literature. This type of scoring system focuses mostly on randomized-controlled trials and does not intend to analyze different types of studies for a systematic review. In anticipation of finding several different types of articles, an original method was developed to encompass multiple designs.

The MURDAD scoring method (appendix) is a more generalized approach to the heterogeneous literature. The MURDAD system is not used as a basis to include or exclude articles, but is a way to give the higher scoring studies more weight when considering the results. This validity measure is based on a ten point scale, as shown in Table Two, which sets the specific criteria to determine a score. ‘Randomization’ is the only criteria worth two points, due to its strength at limiting bias. The rest of the criteria are worth one point. Table Two shows a complete breakdown of how all the articles scored on each MURDAD criterion.

Results

A total of five published articles met the inclusion and exclusion criteria through the systematic review (Table One). The prospective literature included two randomized-controlled trials, one cohort study, and one case-series analysis. One retrospective, multicenter case analysis also met the criteria. The publishing dates ranged from 1990 to 2006. Each study focused on colchicine for the treatment of acute episodes of pericarditis or for preventing recurrence of this condition. Various doses of colchicine were used throughout the studies. For the most part, colchicine was administered in combination with other medications including: NSAIDs, corticosteroids and immunosuppressants. All of the selected studies found colchicine to be effective in the treatment of pericarditis to some degree. Some of the studies also determined that corticosteroids were an independent risk factor for recurrence of pericarditis. Each study will be reviewed separately, discussing the validity (MURDAD score), subject population, specific intervention, comparison groups (where available), outcomes and secondary findings. The articles will be addressed beginning with the highest validity score.

In *Colchicine as First-Choice Therapy for Recurrent Pericarditis* (CORE Trial, 2005), researchers constructed a randomized, open-label study which addressed the safety and efficacy of colchicine as an adjunct to conventional therapy for the first episode of recurrent pericarditis (second episode over-all). The trial consisted of eighty-four subjects with a first episode of recurrent pericarditis. They were randomly assigned to receive aspirin 800 mg orally every six or eight hours for seven to ten days, with gradual tapering for three to four weeks for the control group, or treatment with the same dose of aspirin combined with colchicine for the treatment group. Colchicine was started at 1.0 to 2.0 mg on day one, then 0.5 to 1.0 mg daily for six months as the maintenance dose. The lower dose of colchicine was given to subjects weighing less than 70 kg. When aspirin was not tolerated or contraindicated, prednisone was given at 1.0 to 1.5 mg/kg day for four weeks and gradually tapered. The prednisone patients were distributed equally among the control and treatment groups. Recurrence

rate at eighteen months was the primary endpoint. The colchicine arm had a lower recurrence rate compared to the control group (24.0% vs. 50.6%; $p = 0.02$; NNT=4.0). As a secondary endpoint, the colchicine group appeared to have less symptom persistence at seventy-two hours (10% vs. 31%; $p = 0.03$). Additionally, corticosteroid use was an independent risk factor for recurrence (OR, 2.89; 95% CI, 1.10-8.26; $p = 0.04$). There were no serious adverse reactions observed in the trial. Three patients (7%) discontinued colchicine due to diarrhea. This study received a MURDAD score of eight (Table Two).

In *Colchicine in Addition to Conventional Therapy for Acute Pericarditis* (COPE Trial, 2005), the same authors as the CORE trial formulated another randomized, open-label project to investigate the safety and efficacy of colchicine, when combined with conventional therapy for the treatment of the first episode of acute pericarditis. In this study, 120 subjects with a first episode of acute pericarditis were randomly assigned to conventional treatment for the control group or conventional treatment plus colchicine for the treatment group. Conventional treatment consisted of aspirin 800 mg orally every six or eight hours for seven to ten days, with gradual tapering for three to four weeks. In the treatment group, colchicine was started as 1.0 to 2.0 mg for the first day, then maintained at 0.5 to 1.0 mg/day for three months. Corticosteroids were used in the same manner as the CORE trial and were distributed equally among both groups. The primary endpoint was recurrence rate at eighteen months. Colchicine reduced the recurrence rate at eighteen months (10.7% vs. 32.3%; $p = 0.004$; NNT= 5). It also decreased symptom persistence at seventy-two hours compared to the control group (11.7% vs. 36.7%; $p = 0.003$). Corticosteroid use was again an independent risk factor for recurrence (OR 4.30, 95% CI 1.21 to 15.25; $p = 0.024$). There were no serious adverse reactions observed in the trial. Five subjects (8.3%) discontinued colchicine due to diarrhea. The COPE trial also received a MURDAD score of eight (Table Two).

In *Therapy for Recurrent Acute Pericarditis: A Rheumatological Solution?* (2006), researchers created a prospective, cohort or observational study of fifty-eight patients to assess the safety and

efficacy of a multidrug protocol for the treatment of recurrent pericarditis. All fifty-eight patients were in an active episode of pericarditis and received NSAIDs of an undetermined dosage until they had a complete normalization of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). If patients were taking corticosteroids, the researchers attempted to slowly taper them until discontinuing the medication where possible. Hydroxychloroquine, azathioprine, cyclosporine or methotrexate (undetermined medication or dosage) were initiated if patients had difficulty with corticosteroid tapering. Again, all patients received some form of the multidrug regime described above. With this patient population, forty-four subjects were also treated with colchicine and fourteen were not. Colchicine was started at 0.5 mg daily for seven days, then 1.0 mg daily for one to two years. The primary endpoint was attack rate, which was defined as the number of recurrences each patient had per month (attacks/patient/month). In sum, the study compared the attack rate at the initial visit, at twelve months and at the end of follow-up (8.1 years). After starting the multidrug protocol the attack rate dropped within the whole study from 0.48 to 0.03 attacks/patient/month ($p < 0.00001$) by the first twelve months. It stayed at approximately that same rate until the end of follow-up. The forty-four colchicine patients experienced a decrease in attack rates from 0.54 to 0.03 attacks/patient/month ($p < 0.00001$) at twelve months; and the fourteen non-colchicine patients dropped from 0.31 to 0.06 attacks/patient/month ($p = 0.002$). The decrease in attack rate was higher for the colchicine group (0.51 attacks/patient/month) compared to the control group (0.25 attacks/patient/month) ($p = 0.006$). There were no serious adverse reactions to colchicine. Eight patients (16.3%) discontinued the medication due to side effects: seven from diarrhea and one from an unknown skin-rash. This study received a MURDAD validity score of five (Table Two).

In *Recurrent Pericarditis: Relief with Colchicine* (1990), authors conducted a prospective case-series of nine patients with pericarditis. All of the subjects experienced at least three relapses despite treatment with acetylsalicylic acid, indomethacin, prednisone, or a combination of these medications. Patients were treated with colchicine at 1 mg/day and followed. The length of follow-up for each

patient was different, ranging from ten to fifty-four months. The primary endpoint was the mean interval between recurrences of pericarditis, recorded in months. The researchers found that colchicine increased the time between relapses. Before treatment with colchicine, the mean interval of recurrence was 3.33 +/- 4.3 months. After treatment, the mean interval of recurrence was 24.3 +/- 16.1 months ($p < 0.002$). The subjects had no serious, adverse reactions to colchicine, and no subjects discontinued the medication due to side-effects. The study received a MURDAD score of three (Table Two).

In *Pretreatment with Corticosteroids Attenuates the Efficacy of Colchicine in Preventing Recurrent Pericarditis* (2005), researchers completed a retrospective, multi-center, case-analysis of 119 subjects, by collecting case reports from the previous fifteen years. The subjects studied were required to have at least two documented relapses of pericarditis prior to any reported administration of colchicine. After the two documented relapses, the patients had to have documented treatment with colchicine 1 mg/day. The therapeutic trial of colchicine had to extend beyond any course of NSAIDs or tapering dose of corticosteroids. This retrospective study required complete documented follow-up from the first episode of pericarditis (pre-colchicine), through the trials of colchicine. The researchers compared recurrence rate while on colchicine versus recurrence rate after the discontinuation of the medication. Only 18% (21/119) had recurrences during colchicine therapy and 30% (26/88) after its discontinuation. Researchers identified previous use of corticosteroids (OR 6.68, 95% CI: 1.65-27.02) and male gender (OR 4.20, 95% CI: 1.16-15.21) as independent risk factors for the development of pericarditis. This analysis did not document the number of serious adverse reactions or minor side effects of colchicine. The study received a MURDAD validity score of two (Table Two).

Discussion

The purpose of this paper was to investigate the safety and efficacy of colchicine for the treatment of acute and recurrent pericarditis through a systematic review of the current literature. Five articles from 1990-2006 met the inclusion and exclusion criteria. The key points to discuss in this section are: general safety and efficacy of colchicine, secondary outcomes, validity, and the overall strength of this literature review.

All five studies found colchicine to be effective for the treatment of pericarditis in regards to the stated endpoints. The COPE trial was the only study that had the specific intention of investigating colchicine as the initial treatment of pericarditis in its acute stage.³ The population consisted of 120 subjects with the first episode of acute pericarditis who had never been treated for this condition in the past.³ Colchicine significantly decreased the symptom persistence at seventy-two hours and the recurrence rate at eighteen months (Table One).³ The CORE trial had just a few small differences in study design. This study had eighty-four subjects with a first episode of recurrent pericarditis. These patients had experienced pericarditis on one occasion in the past, and had then suffered a relapse, essentially a second attack. The subjects were maintained on colchicine for six months (COPE trial patients were treated for 3 months).² The CORE trial had the same endpoints. Colchicine had similar results with decreasing the symptom persistence at seventy-two hours and recurrence rate at eighteen months.² In having the same endpoints, both the CORE and COPE trials show the benefit of colchicine for the acute phase and in preventing recurrences of pericarditis. The other three articles focused on the prevention of recurrence with colchicine.^{5, 7, 11} All three of the studies found colchicine to be effective at decreasing the rate of recurrence.

There were no serious, adverse reactions with the use of colchicine reported in any of the articles, although, one study failed to mention the absence or presence of side effects at all. The most

common side effect was diarrhea, which went away shortly after discontinuing the medication.^{2,3,7} An unidentified rash was a rare side effect (occurred in only one patient) that also went away after stopping colchicine.⁷ These results show that colchicine is a fairly safe medication, even when taken long-term.

Three of the five articles found corticosteroids to be an independent risk factor for the recurrence of pericarditis, although there was little discussion as to why this was the case.^{2,3,11} The authors of the COPE trial spent the most time addressing this topic. They speculated that the increase in recurrence rate with the use of corticosteroids may be due to the notion that pericarditis is mostly viral or idiopathic in origin.³ Moreover, corticosteroids may exacerbate the viral process, perpetuating pericardial inflammation and making recurrences more likely.³ While corticosteroids were at one point the treatment of choice for pericarditis, these studies suggest that they may not be the optimum choice, since it seems to make relapse more likely. This finding makes continued study of colchicine, as a safe and effective alternative, all the more imperative.

The COPE and CORE trial were the only randomized studies and had greater strength of evidence with scores of eight. Even the two strongest studies still had potential for significant bias not being of double-blinded design. Additionally, the COPE trial documented five subjects that discontinued colchicine in the treatment arm, and the CORE trial mentioned three who also stopped the medication.³ However, the authors did not explain how this loss was accounted for in the statistical calculations, which could potentially make colchicine appear more efficacious than it really was. None of the remaining three studies were randomized or blinded, and they all received fairly low MURDAD scores. The studies' limitations were typical for the type of study design used. Table Two shows the specific limitations for each article.

The suggestion of colchicine as a treatment for pericarditis is limited by the amount of solid data. There were no double-blinded, randomized-controlled trials, which left all of the studies vulnerable to significant potential bias. Also, with the incidence of pericarditis being rather low

(although unclear) the subject samples were small, decreasing the power of each study. However, all of the studies included in this systematic review found colchicine to be effective in the treatment of pericarditis. There were no serious adverse reactions; the mild side effects that were reported resolved shortly after discontinuing the medication. The results of this systematic review underscore the need for a large, double-blinded, randomized-controlled trial evaluating the efficacy and safety of colchicine in the treatment of pericarditis.

Conclusion

Based on this systematic review of the current literature, there is moderate evidence to support the safety and efficacy of colchicine for the treatment of acute or recurrent pericarditis. A larger, double-blinded, randomized-controlled trial is needed to further evaluate this proposition. There is also evidence to support that corticosteroids are an independent risk factor for the recurrence of pericarditis.

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Tables

Article & Year	Study Type & MURDAD Score	Population	Intervention & Side Effects	Comparison	Outcomes with colchicine	Comments
CORE Trial (2005)	Prospective, randomized, open-label Validity Score = 8	84 patients with a 1st episode of recurrent pericarditis	ASA plus colchicine 0.5-1 mg/d x 6 months 3 patients (7%) stopped colchicine due to diarrhea	Just ASA	Lower recurrence at 18 months 24.0% vs. 50.6% (p=0.02) (NNT=4) Decreased persistence at 72h 10% vs. 31% (p= 0.03)	Corticosteroids independent risk factor OR 2.89 95% CI 1.10-8.26 (p= 0.04) Used when ASA contraindication
COPE Trial (2005)	Prospective, randomized, open-label Validity Score = 8	120 patients with the 1st episode of acute pericarditis	ASA plus colchicine 0.5-1 mg/d x 3 months 5 patients (8.3%) stopped colchicine due to diarrhea	Just ASA	Lower recurrence at 18 months 10.7% vs. 32.3% (p=0.004) (NNT= 5) Decreased persistence at 72h 11.7% vs. 36.7% (p= 0.003)	Corticosteroids independent risk factor OR 4.30 95% CI 1.21-15.25 (p=0.011) Used when ASA contraindication
Therapy for Recurrent Pericarditis: A Rheumatological Solution? (2006)	Prospective Cohort (observational) Study Validity score = 5	58 patients with pericarditis	Multidrug therapy plus colchicine 1mg/d x 1-2 yrs 8 patients (16.3%) stopped colchicine due to diarrhea/skin rash	Multidrug therapy without colchicine	Decreased basal attack rate (attacks/patient/month) colchicine group dropped from 0.54 to 0.03 a/p/m (p<0.00001) Non-colchicine group dropped from 0.31 to 0.06 a/p/m (p=0.002)	
Pretreatment with Corticosteroids Attenuates the Efficacy of Colchicine in Recurrent Pericarditis (2005)	Retrospective, multi-center, case analysis Validity Score = 2	119 patients with pericarditis	colchicine 1mg/d Unknown drop-out due to side-effects	Comparing patient recurrence rate with colchicine and after discontinuing	Decreased recurrence 18% had recurrences with colchicine 30% had recurrences after discontinuation	Corticosteroids independent risk factor OR 6.68 95% CI 1.65-27.02
Recurrent Pericarditis: Relief with Colchicine (1990)	Prospective case series Validity Score = 3	9 patients with pericarditis	colchicine 1 mg/day No drop-out due to side-effects	Length of time between recurrences before/after colchicine	Increased time between recurrences (months) Before tx 3.33 +/- 4.3m After tx 24.3 +/- 16.1 m (p<0.002)	

Table One: Pertinent Data of the Articles Selected

	CORE Trial	COPE Trial	Therapy for Recurrent Acute Pericarditis: A Rheumatological Solution?	Pretreatment with Corticosteroids Attenuates Efficacy of Colchicine in Preventing Recurrent Pericarditis	Recurrent Pericarditis: Relief with Colchicine
Was the study randomized? (2pts)	2	2	0	0	0
Was the study double-blinded? (1pt)	0	0	0	0	0
Sample size of at least 50 subjects? (1pt)	1	1	1	1	0
Well-defined inclusion/exclusion criteria of pericarditis? (1pt)	1	1	1	0	0
Well-defined criteria for remission/recurrence of pericarditis? (1pt)	1	1	1	0	0
Sufficient length of follow-up? (1pt)	1	1	1	0	1
If subjects lost to follow-up, was it accounted for in some way? (1pt)	1	1	1	0	1
Did each subject receive similar treatment other than what was being compared? (1pt)	1	1	0	0	0
Were the subjects similar at the start of the trial? If not, was this accounted for in some way? (1pt)	1	1	0	1	1
Total Points (10pts)	8	8	5	2	3

Table Two: Breakdown of the MURDAD Score for Each Article

Appendix

Criteria	Allowable Points	Points Given
Was the study randomized?	2	
Was the study Double-blinded?	1	
Sample size of at least 50 subjects?	1	
Well-defined inclusion criteria of pericarditis?	1	
Well-defined criteria for recurrence of pericarditis?	1	
Sufficient length of follow-up?	1	
If subjects lost to follow-up, was it accounted for in some way?	1	
Did each subject receive similar treatment other than what was being compared?	1	
Were subjects similar at the start of the trial? If not, was this accounted for in some way?	1	

MURDAD Sample